

In the specification:

Insert the paper copy of the Sequence Listing filed herewith following the Oath/Declaration.

Please amend the paragraph beginning at page 1, line 16, as follows:

a<sup>2</sup>  
An alternate human parathyroid hormone (PTH) receptor, designated as PTH2 receptor, has been identified in rat and human brain. This receptor is selectively activated by PTH-(1-34) (SEQ ID NO:1), but not PTH-related protein PTHrP-(1-34) (SEQ ID NO:2), which has the same calcium-mobilizing activities as PTH-(1-34) (SEQ ID NO:1). Both PTH and PTHrP share a common G protein-coupled receptor, termed the PTH/PTHrP receptor. The PTH2 receptor is localized predominantly in the brain and pancreas, in contrast to PTH/PTHrP receptor, which is primarily localized in bone and the kidney, the principal target tissue for PTH action. Parathyroid hormone (PTH) is the principal physiological regulator of calcium levels in the blood (Chorev, M., Rosenblatt, M., 1994, Structure function analysis of parathyroid hormone and parathyroid hormone-related protein, Bilezikian, J.P., Marcus, R., Levine, M., (eds) The Parathyroids: Basic and Clinical Concepts. Raven Press, New York, pp 139-156; Juppner, H., et al., 1991, Science, 254:1024-1026; and Martin, T.J., et al., 1991, Crit. Rev. Biochem. Mol. Biol. 26:377-395). PTH-related protein (PTHrP) was originally identified as the agent responsible for the paraneoplastic syndrome of humoral hypercalcemia of malignancy (Suva, L.J., et al., 1987, Science, 237:893-896 and Orloff, J.J., et al., 1994, Endocrinol. Rev. 15:40-60). PTH and PTHrP are products of distinct, yet evolutionary-related genes. PTH and PTHrP show sequence similarities only in the N-terminal 13 amino acids, 8 of which are identical (Abou-Samra AB, et al., 1992, Proc. Natl. Sci. Acad. USA, 89:2732-2736). However, the expression pattern and physiological role of these two molecules are remarkably different. PTH has a highly restricted pattern of expression and acts as a classical endocrine hormone, whereas PTHrP is expressed in a wide variety of normal tissues and functions in a predominantly autocrine/paracrine fashion (Urena, P., et al., 1993, Endocrinology, 133:617-623; Lee, K., et al., 1995, Endocrinology, 136:453-463; and Martin, T.J., et al., 1995, Miner. Electrolyte Metab., 21:123-128). More

a2 recently, PTHrP has been shown to play a fundamental role in embryonic differentiation of bone and cartilage development.

Please amend the paragraph beginning at page 3, line 8, as follows:

a3 An homologous receptor for PTH, designated the PTH2 receptor, has been identified and partially characterized (Behar, V., et al., 1996, Endocrinology, 137:2748-2757; Gardella, T.J., et al., 1996, The J. Biol. Chem., 271:19888-19893; Behar, V., et al., 1996, Endocrinology, 137:4217-4224; and Usdin, T.B., et al., 1997, Endocrinology, 138:831-834). Amongst the seven transmembrane G protein-coupled receptors, the PTH2 receptor is most similar in sequence to the PTH/PTHrP receptor (51% of the amino acid sequence identify). Interestingly, PTH2 receptor mRNA is not detected in bone or osteosarcoma cell lines, but is expressed in a number of tissues including the exocrine pancreas, lung, heart, vasculature, and epididymis, and is most abundant in the brain (Usdin, T.B., et al., 1996, Endocrinology, 137:4285-4297). Unlike the PTH/PTHrP receptor, which binds and is activated by both PTH-(1-34) (SEQ ID NO:1) and PTHrP-(1-34) (SEQ ID NO:2), the PTH2 receptor binds and is activated only by PTH-(1-34) (SEQ ID NO:1). [PTHrP (7-34)] PTHrP-(1-34) (SEQ ID NO:2) was found to recognize PTH2 receptor and weakly activate it. Moreover, His<sup>5</sup> in PTHrP was identified as the "specificity switch" for the PTH2 receptor. Swapping a single amino acid, His<sup>5</sup> from PTHrP, with Ile<sup>5</sup> from PTH, resulted in a PTHrP analogue, Ile<sup>5</sup>-PTHrP-(1-34) NH<sub>2</sub> (SEQ ID NO:3), which acts as a PTH-2 receptor agonist. Hence, the single amino acid switch converts inactive PTHrP into a potent PTH2 receptor agonist. But while [Ile<sup>5</sup>] PTHrP (SEQ ID NO:3) binds and activates both receptors, PTH/PTHrP and PTH2, it is not a selective PTH2 agonist. In transient heterologous (with respect to species) expression systems, others have found an additional contribution to hPTH2 receptor selectivity by Trp<sup>23</sup> (Gardella et al., JBC 1996, 271:19888-19893). Like the PTH/PTHrP receptor, PTH binding leads to PTH2 receptor-mediated activation of both cAMP and [Ca<sup>2+</sup>] intracellular signaling pathways.

Please amend the paragraph beginning at page 5, line 8, as follows:

A more preferred PTH analogue that selectively binds to the PTH2 receptor is an analogue of formula (I),  $(R^1R^2)-A^1-A^2-A^3-A^4-A^5-A^6-A^7-A^8-A^9-A^{10}-A^{11}-A^{12}-A^{13}-A^{14}-A^{15}-A^{16}-A^{17}-A^{18}-A^{19}-A^{20}-A^{21}-A^{22}-A^{23}-A^{24}-A^{25}-A^{26}-A^{27}-A^{28}-A^{29}-A^{30}-A^{31}-A^{32}-A^{33}-A^{34}-A^{35}-A^{36}-A^{37}-A^{38}-R^3$ ,

(I)

or a pharmaceutically-acceptable salt thereof wherein

$A^1$  is a hydrophilic or a lipophilic amino acid;

$A^2$  is a lipophilic amino acid;

$A^3$  is a hydrophilic or a lipophilic amino acid;

$A^4$  is a hydrophilic amino acid;

$A^5$  is a hydrophilic or a lipophilic amino acid;

$A^6$  is a hydrophilic amino acid or is deleted;

$A^7$  is a hydrophilic or a lipophilic amino acid or is deleted;

$A^8$  is a lipophilic amino acid or is deleted;

$A^9$  is a hydrophilic amino acid or is deleted;

$A^{10}$  is a hydrophilic amino acid or is deleted;

$A^{11}$  is a hydrophilic or a lipophilic amino acid or is deleted;

$A^{12}$  is a hydrophilic or a lipophilic amino acid or is deleted;

$A^{13}$  is a hydrophilic amino acid;

$A^{14}$  is a hydrophilic amino acid or is deleted;

$A^{15}$  is a lipophilic amino acid or is deleted;

$A^{16}$  is a hydrophilic or a lipophilic amino acid or is deleted;

$A^{17}$  is a hydrophilic or a lipophilic amino acid or is deleted;

$A^{18}$  is a lipophilic amino acid or is deleted;

$A^{19}$  is a hydrophilic or a lipophilic amino acid or is deleted;

$A^{20}$  is a hydrophilic amino acid or is deleted;

$A^{21}$  is a hydrophilic or a lipophilic amino acid or is deleted;

$A^{22}$  is a lipophilic or a hydrophilic amino acid or is deleted;

a4

A<sup>23</sup> is a hydrophilic or a lipophilic amino acid;  
A<sup>24</sup> is a hydrophilic or a lipophilic amino acid;  
A<sup>25</sup> is a hydrophilic amino acid;  
A<sup>26</sup> is a hydrophilic amino acid;  
A<sup>27</sup> is a lipophilic or a hydrophilic amino acid;  
A<sup>28</sup> is a lipophilic amino acid;  
A<sup>29</sup> is a lipophilic or a hydrophilic amino acid;  
A<sup>30</sup> is a hydrophilic or a lipophilic amino acid;  
A<sup>31</sup> is a lipophilic or a hydrophilic amino acid or is deleted;  
A<sup>32</sup> is a hydrophilic amino acid or is deleted;  
A<sup>33</sup> is a hydrophilic amino acid or is deleted;  
A<sup>34</sup> is a lipophilic amino acid or is deleted;  
A<sup>35</sup> is a lipophilic amino acid or is deleted;  
A<sup>36</sup> is a lipophilic or a hydrophilic amino acid or is deleted;  
A<sup>37</sup> is a lipophilic amino acid or is deleted;  
A<sup>38</sup> is a lipophilic or a hydrophilic amino acid or is deleted;

A4  
cont

R<sup>1</sup> and R<sup>2</sup> are each independently selected from the group consisting of H, (C<sub>1</sub>-C<sub>30</sub>)alkyl, (C<sub>2</sub>-C<sub>30</sub>)alkenyl, phenyl-(C<sub>1</sub>-C<sub>30</sub>)alkyl, naphthyl(C<sub>1</sub>-C<sub>30</sub>)alkyl, hydroxy(C<sub>1</sub>-C<sub>30</sub>)alkyl, hydroxy(C<sub>2</sub>-C<sub>30</sub>)alkenyl, hydroxy-phenyl(C<sub>1</sub>-C<sub>30</sub>)alkyl or hydroxy-naphthyl(C<sub>1</sub>-C<sub>30</sub>)alkyl;  
or one of R<sup>1</sup> or R<sup>2</sup> is COE<sup>1</sup> where E<sup>1</sup> is (C<sub>1</sub>-C<sub>30</sub>)alkyl, (C<sub>2</sub>-C<sub>30</sub>)alkenyl, phenyl(C<sub>1</sub>-C<sub>30</sub>)alkyl, naphthyl(C<sub>1</sub>-C<sub>30</sub>)alkyl, hydroxy(C<sub>1</sub>-C<sub>30</sub>)alkyl, hydroxy(C<sub>2</sub>-C<sub>30</sub>)alkenyl, hydroxy-phenyl(C<sub>1</sub>-C<sub>30</sub>)alkyl or hydroxy-naphthyl(C<sub>1</sub>-C<sub>30</sub>)alkyl; and  
R<sup>3</sup> is OH, NH<sub>2</sub>, (C<sub>1</sub>-C<sub>30</sub>)alkoxy or NH-Y-CH<sub>2</sub>-Z, where Y is a (C<sub>1</sub>-C<sub>30</sub>) hydrocarbon moiety and Z is CO<sub>2</sub>H or CONH<sub>2</sub>;

provided that the compound is not PTH(1-34)R<sup>3</sup> (SEQ ID NO:4), PTH(1-35)R<sup>3</sup> (SEQ ID NO:5), PTH(1-36)R<sup>3</sup> (SEQ ID NO:6), PTH(1-37)R<sup>3</sup> (SEQ ID NO:7), or PTH(1-38)R<sup>3</sup> (SEQ ID NO:8).

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Please amend the paragraph beginning at page 7, line 3, as follows:

Another preferred group of PTH analogues that selectively binds to the PTH2 receptor is an analogue of formula (II),  $(R^1R^2)-A^1-A^2-A^3-A^4-A^5-A^6-A^7-A^8-A^9-A^{10}-A^{11}-A^{12}-A^{13}-A^{14}-A^{15}-A^{16}-A^{17}-A^{18}-A^{19}-A^{20}-A^{21}-A^{22}-A^{23}-A^{24}-A^{25}-A^{26}-A^{27}-A^{28}-A^{29}-A^{30}-A^{31}-A^{32}-A^{33}-A^{34}-A^{35}-A^{36}-A^{37}-A^{38}-R^3$ ,

(II)

or a pharmaceutically-acceptable salt thereof wherein

A<sup>1</sup> is Ser, Ala, Dap, Thr, Aib or is deleted;

A<sup>2</sup> is Val, Leu, Ile, Phe, Nle, β-Nal, Aib, p-X-Phe, Acc, Cha, Met or is deleted;

A<sup>3</sup> is Ser, Thr, Aib or is deleted;

A<sup>4</sup> is Glu, Asp or is deleted;

A<sup>5</sup> is Leu, Val, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe, p-X-Phe or is deleted;

A<sup>6</sup> is Gln, a hydrophilic amino acid or is deleted;

A<sup>7</sup> is Leu, Val, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe, p-X-Phe, a lipophilic amino acid, or is deleted;

A<sup>8</sup> is Met, Nva, Leu, Val, Ile, Cha, Acc, Nle, p-X-Phe, Phe, β-Nal, Bpa, a lipophilic amino acid or is deleted;

A<sup>9</sup> is His, a hydrophilic amino acid or is deleted;

A<sup>10</sup> is Asn, a hydrophilic amino acid or is deleted;

A<sup>11</sup> is Leu, Val, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe, p-X-Phe, a hydrophilic amino acid or is deleted;

A<sup>12</sup> is Gly, Acc, Aib, or is deleted;

A<sup>13</sup> is Lys, Arg or HN-CH((CH<sub>2</sub>)<sub>n</sub>NH-R<sup>4</sup>)-C(O);

A<sup>14</sup> is His or is deleted;

A<sup>15</sup> is Leu, Val, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe, p-X-Phe or is deleted;

A<sup>16</sup> is Ser, Asn, Ala, Aib or is deleted;

A<sup>17</sup> is Ser, Thr, Aib or is deleted;

A<sup>18</sup> is Met, Nva, Leu, Val, Ile, Nle, p-X-Phe, Phe, β-Nal, Acc, Cha, Aib or is deleted;

A<sup>19</sup> is Glu, Aib or is deleted;

A<sup>20</sup> is Arg, Lys, HN-CH((CH<sub>2</sub>)<sub>n</sub>NH-R<sup>4</sup>)-C(O) or is deleted;  
A<sup>21</sup> is Val, Leu, Ile, Phe, Nle, β-Nal, Aib, p-X-Phe, Acc, Cha, Met or is deleted;  
A<sup>22</sup> is Acc, Aib, Glu or is deleted;  
A<sup>23</sup> is Trp, Acc, Phe, p-X-Phe, Aib, β-Nal or Cha;  
A<sup>24</sup> is Leu, Acc, Ile, Val, Phe, β-Nal, Nle, Aib, p-X-Phe or Cha;  
A<sup>25</sup> is Arg, Lys or HN-CH((CH<sub>2</sub>)<sub>n</sub>NH-R<sup>4</sup>)-C(O);  
A<sup>26</sup> is Arg, Lys or HN-CH((CH<sub>2</sub>)<sub>n</sub>NH-R<sup>4</sup>)-C(O);  
A<sup>27</sup> is Lys, Aib, Leu, hArg, Gln, Acc, Arg, Cha, Nle, Ile, Val, Phe, β-Nal, or p-X-Phe, where the Lys is optionally substituted on the ε-amino group by an acyl group;  
A<sup>28</sup> is Leu, Acc, Cha, Ile, Val, Phe, Nle, β-Nal, Aib or p-X-Phe;  
A<sup>29</sup> is Gln, Acc or Aib;  
A<sup>30</sup> is Asp, Lys, Arg or is deleted;  
A<sup>31</sup> is Val, Leu, Nle, Acc, Cha, Phe, Ile, β-Nal, Aib, p-X-Phe or is deleted;  
A<sup>32</sup> is His or is deleted;  
A<sup>33</sup> is Asn or is deleted;  
A<sup>34</sup> is Phe, Tyr, Amp, Aib, β-Nal, Cha, Nle, Leu, Ile, Acc, p-X-Phe or is deleted;  
A<sup>35</sup> is Val, Leu, Nle, Acc, Cha, Phe, Ile, β-Nal, Aib, p-X-Phe or is deleted;  
A<sup>36</sup> is Ala, Val, Aib, Acc, Nva, Abu or is deleted;  
A<sup>37</sup> is Leu, Val, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe, p-X-Phe, a lipophilic amino acid, or is deleted;  
A<sup>38</sup> is Gly, Acc, Aib, or is deleted;

where X for each occurrence is independently selected from the group consisting of OH, a halo and CH<sub>3</sub>;

R<sup>1</sup> and R<sup>2</sup> are each independently selected from the group consisting of H, (C<sub>1</sub>-C<sub>30</sub>)alkyl, (C<sub>2</sub>-C<sub>30</sub>)alkenyl, phenyl-(C<sub>1</sub>-C<sub>30</sub>)alkyl, naphthyl(C<sub>1</sub>-C<sub>30</sub>)alkyl, hydroxy(C<sub>1</sub>-C<sub>30</sub>)alkyl, hydroxy(C<sub>2</sub>-C<sub>30</sub>)alkenyl, hydroxy-phenyl(C<sub>1</sub>-C<sub>30</sub>)alkyl or hydroxy-naphthyl(C<sub>1</sub>-C<sub>30</sub>)alkyl;

as  
cont

or one of R<sup>1</sup> or R<sup>2</sup> is COE<sup>1</sup> where E<sup>1</sup> is (C<sub>1</sub>-C<sub>30</sub>)alkyl, (C<sub>2</sub>-C<sub>30</sub>)alkenyl, phenyl(C<sub>1</sub>-C<sub>30</sub>)alkyl, naphthyl(C<sub>1</sub>-C<sub>30</sub>)alkyl, hydroxy(C<sub>1</sub>-C<sub>30</sub>)alkyl, hydroxy(C<sub>2</sub>-C<sub>30</sub>)alkenyl, hydroxy-phenyl(C<sub>1</sub>-C<sub>30</sub>)alkyl or hydroxy-naphthyl(C<sub>1</sub>-C<sub>30</sub>)alkyl;

R<sup>3</sup> is OH, NH<sub>2</sub>, (C<sub>1</sub>-C<sub>30</sub>)alkoxy or NH-Y-CH<sub>2</sub>-Z, where Y is a (C<sub>1</sub>-C<sub>30</sub>) hydrocarbon moiety and Z is CO<sub>2</sub>H or CONH<sub>2</sub>;

n for each occurrence is independently an integer from 1 to 5; and

R<sup>4</sup> for each occurrence is independently (C<sub>1</sub>-C<sub>30</sub>)alkyl, (C<sub>1</sub>-C<sub>30</sub>)acyl or -C((NH)(NH<sub>2</sub>));

provided that the compound is not PTH(1-34)R<sup>3</sup> (SEQ ID NO:4), PTH(1-35)R<sup>3</sup> (SEQ ID NO:5), PTH(1-36)R<sup>3</sup> (SEQ ID NO:6), PTH(1-37)R<sup>3</sup> (SEQ ID NO:7), or PTH(1-38)R<sup>3</sup> (SEQ ID NO:8).

Please amend the paragraph beginning at page 9, line 11, as follows:

In another respect, this invention provides a PTHrP analogue that selectively binds to the PTH2 receptor of the formula (IV), (R<sup>1</sup>R<sup>2</sup>)-A<sup>1</sup>-A<sup>2</sup>-A<sup>3</sup>-A<sup>4</sup>-A<sup>5</sup>-A<sup>6</sup>-A<sup>7</sup>-A<sup>8</sup>-A<sup>9</sup>-A<sup>10</sup>-A<sup>11</sup>-A<sup>12</sup>-A<sup>13</sup>-A<sup>14</sup>-A<sup>15</sup>-A<sup>16</sup>-A<sup>17</sup>-A<sup>18</sup>-A<sup>19</sup>-A<sup>20</sup>-A<sup>21</sup>-A<sup>22</sup>-A<sup>23</sup>-A<sup>24</sup>-A<sup>25</sup>-A<sup>26</sup>-A<sup>27</sup>-A<sup>28</sup>-A<sup>29</sup>-A<sup>30</sup>-A<sup>31</sup>-A<sup>32</sup>-A<sup>33</sup>-A<sup>34</sup>-A<sup>35</sup>-A<sup>36</sup>-A<sup>37</sup>-A<sup>38</sup>-R<sup>3</sup>,

(IV)

or a pharmaceutically acceptable salt thereof, wherein

A<sup>1</sup> is Ala, Ser, Dap, Thr, Aib or is deleted;

A<sup>2</sup> is Val or is deleted;

A<sup>3</sup> is Ser, Aib, Thr or is deleted;

A<sup>4</sup> is Glu, Asp or is deleted;

A<sup>5</sup> is His, Ile, Acc, Val, Nle, Phe, Leu, p-X-Phe, β-Nal, Aib, Cha or is deleted;

A<sup>6</sup> is Gln, a hydrophilic amino acid or is deleted;

A<sup>7</sup> is Leu, Val, Cha, Nle, β-Nal, Trp, Pal, Acc, Phe, p-X-Phe, Aib, a lipophilic amino acid or is deleted;

A<sup>8</sup> is Leu, Met, Acc, Cha, Aib, Nle, Phe, Ile, Val, β-Nal, p-X-Phe, a lipophilic amino acid or is deleted;

A<sup>9</sup> is His, a hydrophilic amino acid or is deleted;

A<sup>10</sup> is Asp, Asn, a hydrophilic amino acid or is deleted;

A<sup>11</sup> is Lys, Arg, Leu, Cha, Aib, p-X-Phe, Ile, Val, Nle, Acc, Phe,  $\beta$ -Nal, HN-CH((CH<sub>2</sub>)<sub>n</sub>NH-R<sup>4</sup>)-C(O), a lipophilic D-amino acid, a hydrophilic amino acid or is deleted;

A<sup>12</sup> is Gly, Acc, Aib or is deleted;

A<sup>13</sup> is Lys, Arg, HN-CH((CH<sub>2</sub>)<sub>n</sub>NH-R<sup>4</sup>)-C(O) or is deleted;

A<sup>14</sup> is Ser, His or is deleted;

A<sup>15</sup> is Ile, Acc, Cha, Leu, Phe, Nle,  $\beta$ -Nal, Trp, p-X-Phe, Val, Aib or is deleted;

A<sup>16</sup> is Gln, Aib or is deleted;

A<sup>17</sup> is Asp, Aib or is deleted;

A<sup>18</sup> is Leu, Aib, Acc, Cha, Phe, Ile, Nle,  $\beta$ -Nal, Val, p-X-Phe or is deleted;

A<sup>19</sup> is Arg, Lys, Aib, HN-CH((CH<sub>2</sub>)<sub>n</sub>NH-R<sup>4</sup>)-C(O) or is deleted;

A<sup>20</sup> is Arg, Lys, HN-CH((CH<sub>2</sub>)<sub>n</sub>NH-R<sup>4</sup>)-C(O) or is deleted;

A<sup>21</sup> is Arg, Lys, HN-CH((CH<sub>2</sub>)<sub>n</sub>NH-R<sup>4</sup>)-C(O) or is deleted;

A<sup>22</sup> is Phe, Glu, Aib, Acc, p-X-Phe,  $\beta$ -Nal, Val, Leu, Ile, Nle or Cha;

A<sup>23</sup> is Phe, Leu, Lys, Acc, Cha,  $\beta$ -Nal, Aib, Nle, Ile, p-X-Phe, Val or Trp;

A<sup>24</sup> is Leu, Lys, Acc, Nle, Ile, Val, Phe,  $\beta$ -Nal, Aib, p-X-Phe, Arg or Cha;

A<sup>25</sup> is His, Lys, Aib, Acc, Arg or Glu;

A<sup>26</sup> is His, Aib, Acc, Arg or Lys;

A<sup>27</sup> is Leu, Lys, Acc, Arg, Ile, Val, Phe, Aib, Nle,  $\beta$ -Nal, p-X-Phe or Cha;

A<sup>28</sup> is Ile, Leu, Lys, Acc, Cha, Val, Phe, p-X-Phe, Nle,  $\beta$ -Nal, Aib or is deleted;

A<sup>29</sup> is Ala, Glu, Acc, Aib or is deleted;

A<sup>30</sup> is Glu, Leu, Nle, Cha, Aib, Acc, Lys, Arg or is deleted;

A<sup>31</sup> is Ile, Leu, Cha, Lys, Acc, Phe, Val, Nle,  $\beta$ -Nal, Arg or is deleted;

A<sup>32</sup> is His or is deleted;

A<sup>33</sup> is Thr, Ser or is deleted;

A<sup>34</sup> is Ala, Phe, Tyr, Cha, Val, Ile, Leu, Nle,  $\beta$ -Nal, Aib, Acc or is deleted;

A<sup>35</sup> is Glu, Asp or is deleted;

A<sup>36</sup> is Ile, Acc, Cha, Leu, Phe, Nle,  $\beta$ -Nal, Trp, p-X-Phe, Val, Aib or is deleted;

A<sup>37</sup> is Arg, Lys, HN-CH((CH<sub>2</sub>)<sub>n</sub>NH-R<sup>4</sup>)-C(O) or is deleted;

A<sup>38</sup> is Ala, Phe, Tyr, Cha, Val, Ile, Leu, Nle,  $\beta$ -Nal, Aib, Acc or is deleted;

Ab  
Cont



*a6*

$R^1$  and  $R^2$  are each independently selected from the group consisting of H, (C<sub>1</sub>-C<sub>30</sub>)alkyl, (C<sub>2</sub>-C<sub>30</sub>)alkenyl, phenyl-(C<sub>1</sub>-C<sub>30</sub>)alkyl, naphthyl(C<sub>1</sub>-C<sub>30</sub>)alkyl, hydroxy(C<sub>1</sub>-C<sub>30</sub>)alkyl, hydroxy(C<sub>2</sub>-C<sub>30</sub>)alkenyl, hydroxy-phenyl(C<sub>1</sub>-C<sub>30</sub>)alkyl or hydroxy-naphthyl(C<sub>1</sub>-C<sub>30</sub>)alkyl;  
or one of  $R^1$  or  $R^2$  is COE<sup>1</sup> where E<sup>1</sup> is (C<sub>1</sub>-C<sub>30</sub>)alkyl, (C<sub>2</sub>-C<sub>30</sub>)alkenyl, phenyl(C<sub>1</sub>-C<sub>30</sub>)alkyl, naphthyl(C<sub>1</sub>-C<sub>30</sub>)alkyl, hydroxy(C<sub>1</sub>-C<sub>30</sub>)alkyl, hydroxy(C<sub>2</sub>-C<sub>30</sub>)alkenyl, hydroxy-phenyl(C<sub>1</sub>-C<sub>30</sub>)alkyl or hydroxy-naphthyl(C<sub>1</sub>-C<sub>30</sub>)alkyl;  
 $R^3$  is OH, NH<sub>2</sub>, (C<sub>1</sub>-C<sub>30</sub>)alkoxy or NH-Y-CH<sub>2</sub>-Z, where Y is a (C<sub>1</sub>-C<sub>30</sub>) hydrocarbon moiety and Z is CO<sub>2</sub>H or CONH<sub>2</sub>;  
n for each occurrence is independently an integer from 1 to 5; and  
 $R^4$  for each occurrence is independently (C<sub>1</sub>-C<sub>30</sub>)alkyl, (C<sub>1</sub>-C<sub>30</sub>)acyl or -C((NH)(NH<sub>2</sub>));

provided that the compound is not PTHrP(1-34) $R^3$  (SEQ ID NO:9), PTHrP(1-35) $R^3$  (SEQ ID NO:10), PTHrP(1-36) $R^3$  (SEQ ID NO:11), PTHrP(1-37) $R^3$  (SEQ ID NO:12) or PTHrP(1-38) $R^3$  (SEQ ID NO:13), and further provided that the compound is not [Ile<sup>5</sup>, Trp<sup>23</sup>] PTHrP(1-36) (SEQ ID NO:14) or [Trp<sup>23</sup>] PTHrP(1-36) (SEQ ID NO:15).

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Please amend the paragraph beginning at page 14, line 9, as follows:

*a7*

A preferred group of compounds of formula (III) are the compounds listed as Examples 1-73, shown hereinbelow. Of the compounds listed as Examples 1-73, the following compounds are preferred: [Cha<sup>7,11</sup>, des-Met<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH-(1-34)NH<sub>2</sub> (SEQ ID NO:16), [Cha<sup>7,11</sup>, D-Nle<sup>8</sup>, des-Met<sup>18</sup>, Tyr<sup>34</sup>]hPTH-(1-34)NH<sub>2</sub>, [Cha<sup>7,11</sup>, D-Nle<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH-(1-34)NH<sub>2</sub>, [D-Nle<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub> and [D-Bpa<sup>8</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>.

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Please amend the paragraph beginning at page 20, line 3, as follows:

*a8*

A peptide of this invention is also denoted herein by another format, e.g., [D-Nle<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>, with the substituted amino acids from the natural sequence placed between the set of brackets (e.g., D-Nle<sup>8</sup> for Met<sup>8</sup> in hPTH). The abbreviation hPTH stands for human PTH, and hPTHrP for human PTHrP. The numbers between the parentheses refer to the number of amino acids present in the peptide (e.g., hPTH(1-34) is amino acids 1 through 34 of

a<sup>8</sup> the peptide sequence for human PTH; SEQ ID NO:1). The sequences for hPTH(1-34) (SEQ ID NO:1) and hPTHrP(1-34) (SEQ ID NO:2) are listed in Nissenson, et al., Receptor, 3:193 (1993). The designation "NH<sub>2</sub>" in PTH(1-34)NH<sub>2</sub> (SEQ ID NO:53) indicates that the C-terminus of the peptide is amidated. PTH(1-34) (SEQ ID NO:1) means that the C-terminus is the free acid.

Please amend the paragraph beginning at page 21, line 37, as follows:

a<sup>9</sup> Receptor binding assay: Ligand binding is performed using Saos-2/B-10, HEK/C-21 cells or HEK/BP-16 cells using HPLC-purified [<sup>125</sup>I][Nle<sup>8,18</sup>, Tyr<sup>34</sup>]bPTH-(1-34)NH<sub>2</sub> (<sup>125</sup>I-PTH) (SEQ ID NO:17) as radioligand. Saos-2 cells are maintained for four days until they reach confluence. The medium is replaced with 5% FBS in RPMI 1640 medium and incubated for about 2 hrs at room temperature with 10 x 10<sup>4</sup> cpm mono-<sup>125</sup>I-[Nle<sup>8,18</sup>, Tyr<sup>34</sup>(3-<sup>125</sup>I)]bPTH(1-34)NH<sub>2</sub> (SEQ ID NO:17) in the presence of competing peptides of the invention at various concentrations between 10<sup>-11</sup>M to 10<sup>-4</sup>M. The cells are washed four times with ice-cold PBS and lysed with 0.1 M NaOH, and the radioactivity associated with the cells is counted in a scintillation counter. Synthesis of mono-<sup>125</sup>I-[Nle<sup>8,18</sup>, Tyr<sup>34</sup>(3-<sup>125</sup>I)]bPTH(1-34)NH<sub>2</sub> (SEQ ID NO:17) is carried out as described in Goldman, M.E., et al., Endocrinol., 123:1468 (1988).

Please amend the paragraph beginning at page 22, line 14, as follows:

a<sup>10</sup> The binding assay is conducted with various peptides of the invention, and the K<sub>d</sub> value (half maximal inhibition of binding of mono-<sup>125</sup>I-[Nle<sup>8,18</sup>, Tyr<sup>34</sup>(3-<sup>125</sup>I)]bPTH(1-34)NH<sub>2</sub> (SEQ ID NO:17)) for each peptide is calculated.

Please amend the table beginning at page 29, line 15, as follows:

a<sup>11</sup>

Example	Name	Mass Spec.
3	[Cha <sup>7,11</sup> , des-Met <sup>8</sup> , Nle <sup>18</sup> , Tyr <sup>34</sup> ]hPTH(1-34)NH <sub>2</sub> ( <u>SEQ ID NO:16</u> )	4063.5
4	[Cha <sup>7,11</sup> , D-Nle <sup>8</sup> , des-Met <sup>18</sup> , Tyr <sup>34</sup> ]hPTH(1-34)NH <sub>2</sub>	4063.4
5	[D-Bpa <sup>8</sup> , Tyr <sup>34</sup> ]hPTH-(1-34)NH <sub>2</sub>	4320.7

Please amend the paragraph beginning at page 29, line 21, as follows:

Examples 6 to 86 can be synthesized substantially according to the procedure of

Example 1 using the appropriate, protected amino acids.

Example 6: [D-Nle<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>

Example 7: [D-Nle<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>

Example 8: [D-Leu<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>

Example 9: [D-Cha<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>

Example 10: [D-Phe<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>

Example 11: [D-Nal<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>

Example 12: [D-Abu<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>

Example 13: [D-Met<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>

Example 14: [Cha<sup>7,11</sup>, D-Met<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>

Example 15: [D-Ile<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>

Example 16: [Cha<sup>7,11</sup>, D-Ile<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>

Example 17: [D-Ile<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>

Example 18: [D-Leu<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>

Example 19: [Cha<sup>7,11</sup>, D-Leu<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>

Example 20: [D-Val<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>

Example 21: [Cha<sup>7,11</sup>, D-Val<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>

Example 22: [D-Val<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>

Example 23: [D-Cha<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>

Example 24: [Cha<sup>7,11</sup>, D-Cha<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>

Example 25: [D-Ala<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>

Example 26: [Cha<sup>7,11</sup>, D-Ala<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>

Example 27: [D-Ala<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>

Example 28: [D-Phe<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>

Example 29: [Cha<sup>7,11</sup>, D-Phe<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>

Example 30: [D-Met<sup>8</sup>]hPTH(7-34)NH<sub>2</sub>

Example 31: [D-Nal<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>

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- Example 32: [D-Trp<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>
- Example 33: [Cha<sup>7,11</sup>, D-Trp<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>
- Example 34: [D-Trp<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>
- Example 35: [D-Abu<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>
- Example 36: [Cha<sup>7,11</sup>, D-Abu<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>
- Example 37: [des-Met<sup>8</sup>]hPTH(1-34)NH<sub>2</sub> (SEQ ID NO:18)
- Example 38: [Cha<sup>7,11</sup>, des-Met<sup>8</sup>]hPTH(1-34)NH<sub>2</sub> (SEQ ID NO:19)
- Example 39: [Cha<sup>7,11</sup>, des-Met<sup>8</sup>, des-Met<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub> (SEQ ID NO:20)
- Example 40: [des-Met<sup>8</sup>, des-Met<sup>18</sup>]hPTH(1-34)NH<sub>2</sub> (SEQ ID NO:21)
- Example 41: [Cha<sup>7,11</sup>, des-Met<sup>8</sup>, des-Met<sup>18</sup>]hPTH(1-34)NH<sub>2</sub> (SEQ ID NO:22)
- Example 42: [des-Met<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub> (SEQ ID NO:23)
- Example 43: [des-Met<sup>18</sup>]hPTH(1-34)NH<sub>2</sub> (SEQ ID NO:24)
- Example 44: [Cha<sup>7,11</sup>, des-Met<sup>18</sup>]hPTH(1-34)NH<sub>2</sub> (SEQ ID NO:25)
- Example 45: [Cha<sup>7,11</sup>, des-Met<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub> (SEQ ID NO:26)
- Example 46: [D-Nle<sup>8</sup>, des-Met<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>
- Example 47: [des-Glu<sup>6</sup>Gln<sup>6</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub> (SEQ ID NO:27)
- Example 48: [des-Leu<sup>7</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub> (SEQ ID NO:28)
- Example 49: [des-His<sup>9</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub> (SEQ ID NO:29)
- Example 50: [des-Asn<sup>10</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub> (SEQ ID NO:30)
- Example 51: [des-Leu<sup>11</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub> (SEQ ID NO:31)
- Example 52: [des-Gly<sup>12</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub> (SEQ ID NO:32)
- Example 53: [des-Lys<sup>13</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub> (SEQ ID NO:33)
- Example 54: [des-His<sup>14</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub> (SEQ ID NO:34)
- Example 55: [des-Leu<sup>15</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub> (SEQ ID NO:35)
- Example 56: [des-Asn<sup>16</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub> (SEQ ID NO:36)
- Example 57: [des-Ser<sup>17</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub> (SEQ ID NO:37)
- Example 58: [des-Glu<sup>19</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub> (SEQ ID NO:38)
- Example 59: [des-Arg<sup>20</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub> (SEQ ID NO:39)
- Example 60: [des-Val<sup>21</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub> (SEQ ID NO:40)
- Example 61: [des-Glu<sup>22</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub> (SEQ ID NO:41)

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cm4

- Example 62: [des-Glu<sup>6</sup>Gln<sup>6</sup>, Cha<sup>7,11</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub> (SEQ ID NO:42)
- Example 63: [des-Leu<sup>7</sup>, Nle<sup>8,18</sup>, Cha<sup>11</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub> (SEQ ID NO:43)
- Example 64: [Cha<sup>7,11</sup>, des-His<sup>9</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub> (SEQ ID NO:44)
- Example 65: [des-Glu<sup>6</sup>Gln<sup>6</sup>, Cha<sup>7,11</sup>, D-Nle<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>
- Example 66: [des-Leu<sup>7</sup>, D-Nle<sup>8</sup>, Cha<sup>11</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>
- Example 67: [Cha<sup>7,11</sup>, D-Nle<sup>8</sup>, des-His<sup>9</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>
- Example 68: [Cha<sup>7,11</sup>, des-Met<sup>8</sup>, des-His<sup>9</sup>, des-Asn<sup>10</sup>]hPTH(1-34)NH<sub>2</sub> (SEQ ID NO:45)
- Example 69: [Cha<sup>7,11</sup>, des-Ser<sup>17</sup>, des-Met<sup>18</sup>, des-Glu<sup>19</sup>]hPTH(1-34)NH<sub>2</sub> (SEQ ID NO:46)
- Example 70: [D-Met<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>
- Example 71: [D-Met<sup>8</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>
- Example 72: [D-Nle<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(7-34)NH<sub>2</sub>
- Example 73: [D-Nle<sup>8</sup>, Nle<sup>18</sup>]hPTH(7-34)NH<sub>2</sub>
- Example 74: [Ile<sup>5</sup>, D-Leu<sup>8</sup>]hPTHrP(1-34)NH<sub>2</sub>
- Example 75: [Ile<sup>5</sup>, D-Leu<sup>8</sup>, Trp<sup>23</sup>]hPTHrP(1-34)NH<sub>2</sub>
- Example 76: [Ile<sup>5</sup>, des-Leu<sup>8</sup>, Trp<sup>23</sup>]hPTHrP(1-34)NH<sub>2</sub> (SEQ ID NO:47)
- Example 77: [Ile<sup>5</sup>, des-Leu<sup>8</sup>]hPTHrP(1-34)NH<sub>2</sub> (SEQ ID NO:48)
- Example 78: [des-Leu<sup>8</sup>, Trp<sup>23</sup>]hPTHrP(1-34)NH<sub>2</sub> (SEQ ID NO:49)
- Example 79: [Ile<sup>5</sup>, des-Leu<sup>18</sup>]hPTHrP(1-34)NH<sub>2</sub> (SEQ ID NO:50)
- Example 80: [Ile<sup>5</sup>, des-Leu<sup>18</sup>, Trp<sup>23</sup>]hPTHrP(1-34)NH<sub>2</sub> (SEQ ID NO:51)
- Example 81: [des-Leu<sup>18</sup>, Trp<sup>23</sup>]hPTHrP(1-34)NH<sub>2</sub> (SEQ ID NO:52)
- Example 82: [Ile<sup>5</sup>, D-Leu<sup>8</sup>, Glu<sup>22,25</sup>, Leu<sup>23,28,31</sup>, Lys<sup>26,30</sup>, Aib<sup>29</sup>]hPTHrP(1-34)NH<sub>2</sub>
- Example 83: [Ile<sup>5</sup>, D-Leu<sup>8</sup>, Glu<sup>22,25</sup>, Trp<sup>23</sup>, Lys<sup>26,30</sup>, Leu<sup>28,31</sup>, Aib<sup>29</sup>]hPTHrP(1-34)NH<sub>2</sub>
- Example 84: [Ile<sup>5</sup>, D-Leu<sup>8</sup>, Glu<sup>22,25,29</sup>, Leu<sup>23,28,31</sup>, Lys<sup>26,30</sup>]hPTHrP(1-34)NH<sub>2</sub>
- Example 85: [Ile<sup>5</sup>, D-Leu<sup>8</sup>, Glu<sup>22,25,29</sup>, Trp<sup>23</sup>, Lys<sup>26,30</sup>, Leu<sup>28,31</sup>]hPTHrP(1-34)NH<sub>2</sub>
- Example 86: [D-Leu<sup>8</sup>, Trp<sup>23</sup>]hPTHrP(7-34)NH<sub>2</sub>
-